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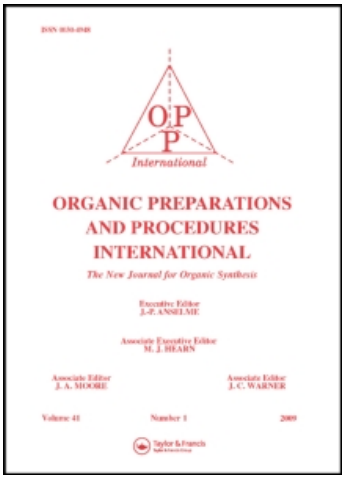

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SYNTHESIS OF NEW ARYL AND HETEROAROMATIC SUBSTITUTED PYRIDINES, PYRAZOLES, PYRIMIDINES AND PYRAZOLO[3,4-D]PYRIDAZINES

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SYNTHESIS OF NEW ARYL AND HETEROAROMATIC SUBSTITUTED PYRIDINES, PYRAZOLES, PYRIMIDINES AND PYRAZOLO[3,4-D]PYRIDAZINES

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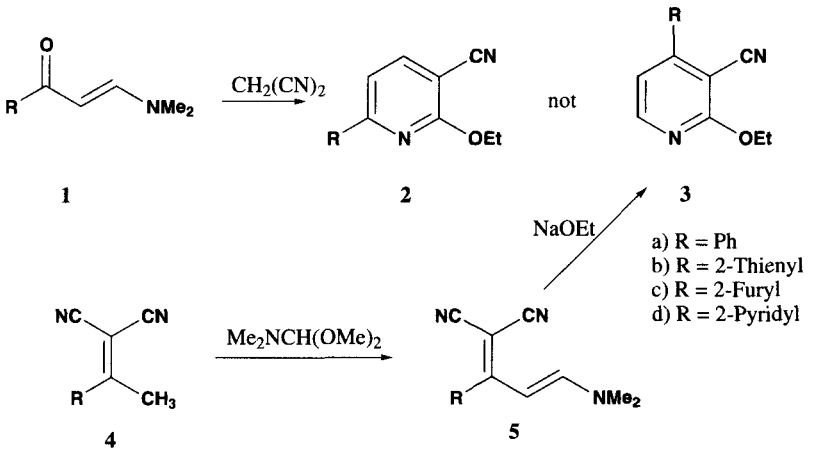
As a part of a program aimed at the synthesis of functionally substituted azoles and azines as potential biodegradable agrochemicals,[1-3] samples of pyridines, pyrazoles, pyrimidines and pyrazolo[3,4-d]pyridazines with aryl and heteroaromatic substituents were required. 3-Aminoenones have been extensively utilized for the synthesis of pyrans,[4] pyridines,[5] pyrazoles[5,8] and isoxazoles[7,9] by addition of malonic acid derivatives,[10,11] hydrazine[5,8] and hydroxylamine[9] to the α,β-unsaturated linkage and subsequent cyclization. The present paper reports on the utilization of these methods for the synthesis of the required compounds.

Compounds **1b-d** were prepared by condensation of methyl ketones with dimethylformamide dimethylacetal utilizing the literature procedure for the synthesis of **la.**[12] Compounds **la-d** react with malononitrile in refluxing ethanolic sodium ethoxide to yield products that may be formulated as the ethoxypyridines **2a-d** or **3a-d** (Scheme 1). Thus, addition of malononitrile across the activated double bond in **1a-d** would yield the Michael adducts; addition of ethanol to yield the iminoethers is finally followed by cyclization to yield products **2a-d**.



Scheme 1

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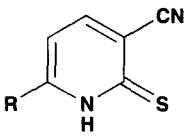
Structure **2** was established for the reaction products based on non-identity of **2b,c** with samples of **3b,c** prepared by condensation of **4b,c** with dimethylformamide dimethylacetal and subsequent treatment of the formed **5b,c** with sodium ethoxide utilizing our recently reported procedure.[13] Moreover, spectral data for the reaction products are in complete accordance with the proposed structures. The formation of **2a-d** from **1a-d** and malononitrile is thus a further extension of the ethoxypyridine synthesis from the reaction of chalcones with malononitrile or the reaction of methyl ketones with arylidenemalononitrile.[14-16]

Compounds **1a,c** reacted with cyanothioacetamide in ethanolic sodium ethoxide at reflux to yield the 2-thioxopyridine-3-carbonitriles **6a-c**. Compounds **6a,c** are assumed to be formed by addition of active methylene of the cyanothioacetamide to the activated double bond in **1a,c** followed by



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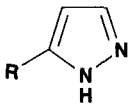
a) R = Ph
b) R = 2-Thienyl
c) R = 2-Furyl



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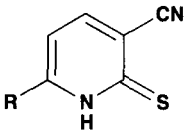
R = 2-Thienyl



8

a) R = Ph
b) R = 2-Thienyl
c) R = 2-Furyl

cyclization and dimethylamine elimination to yield **6a,c**. Compound **1b** reacted with hydrazine to yield the pyrazole **7** and the reactions of **1a-c** with thiourea in refluxing sodium ethoxide yielded the pyrimidine-2-thiones **8a-c**.

Nitrilimines, generated by action of bases on hydrazonyl halides have been reported to add to α,β-unsaturated carbonyl compounds to yield mixtures of isomeric pyrazolines.[17] In the present work, the reaction of nitrilimine **10** (generated from **9** and triethylamine) with **1b** has afforded only one pyrazole derivative by cycloaddition and dimethylamine elimination. This derivative may be formulated as **11** or its isomer **12.** Structure **11** was established based on conversion of the product of reaction of **10** and **1b** with hydrazine hydrate into the pyrazolo[3,4-d]pyridazine **13.** Clearly this product could not be obtained from **12** (Scheme 2).

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR were recorded on a Bruker AC-80 spectrometer in DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standards; chemical shifts are reported in δ units (ppm), coupling constants are given in Hz. Mass spectra were measured on GS/MS INCOS LXL Finnigan MAT. Microanalyses were performed on a Leco CHNS-932

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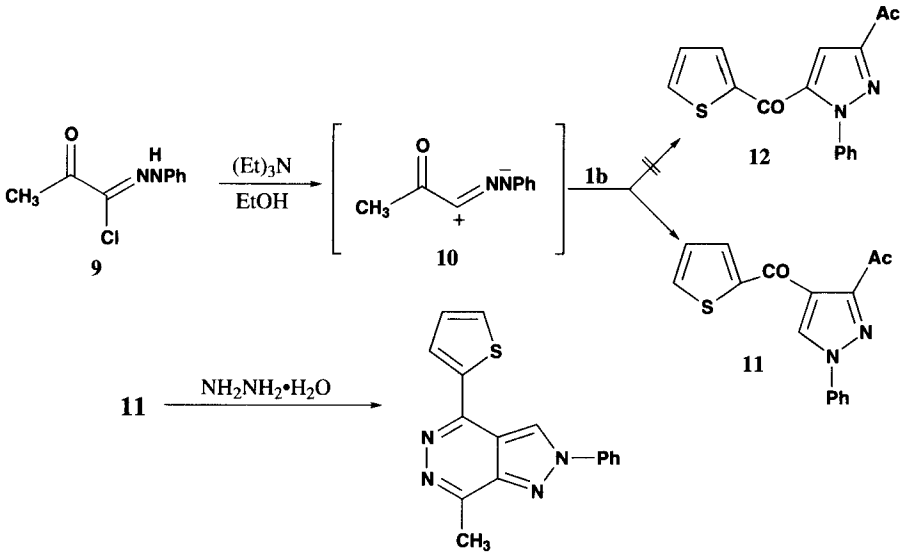

Scheme 2

General Procedures:

3-Dimethylamino-1-substituted-2-propenone (1a-d).- A suspension of the appropriate aryl methyl ketones (0.01 mol) in *p*-xylene (50 mL) was treated with dimethylformamide dimethylacetal (0.01 mol, 1.3 mL). The reaction mixture was refluxed for 7 hrs. The *p*-xylene was then evaporated and the remaining product triturated with petroleum ether (40-60°). The resulting solid product, was collected and crystallized from ethanol.

2-Ethoxy-6-substituted-pyridine-3-carbonitrile (2a-d).- A mixture of each of **1a-d** (0.01 mol) and malononitrile (0.01 mol) in absolute ethanol (50 mL) was treated with a solution of sodium ethoxide (prepared from 0.6 sodium metal and 60 mL of ethanol). The reaction mixture was refluxed for 3 hrs, then poured into ice cold water and neutralized with HCl (10%). The solid product which formed was collected by filtration and crystallized from ethanol.

1,2-Dihydro-6-Substituted-2-thioxopyridine-3-carbonitrile (6a-c).- A mixture of **1a-c** (0.01 mol) and cyanothioacetamide (0.01 mol, 1.2 g) was refluxed in sodium ethoxide solution (prepared from 0.6 g sodium metal and 60 mL ethanol), was refluxed for 3-4 hrs, then poured into ice cold water, and neutralized with HCl. The resulting solid product, was collected by filtration and crystallized from a mixture of ethanol and dimethylformamide (1:1).

3-(2-Thienyl)-(2H)-pyrazole (7).- A mixture of **1b** (0.01 mol;) and hydrazine hydrate (0.01 mol, 0.5 mL) in ethanol (50 mL) was refluxed for 3 hrs. The reaction mixture was concentrated under vacum and left to cool. The solid product was collected and crystallized from ethanol.

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TABLE 1. Yields, mps, Color and Elemental Analyses for Compounds **1a-d**, **2a-d**, **6a-c**, **7**, **8a-c**, **11** and **13**

Cmpd No.	Yield (%)	mp. (°C)	Color	Elemental Analyses (Found) C	H	N	S
1a[a]	72	86-88	yellow	75.39 (75.14)	7.47 (7.51)	7.99 (8.00)	
1b	75	108-110	yellow	59.63 (59.34)	6.11 (6.07)	7.72 (7.57)	
1c	69	84-86	yellow	65.43 (65.52)	6.71 (6.70)	8.47 (8.47)	
1d	75	126-128	yellow	68.15 (68.25)	6.86 (6.83)	15.89 (15.82)	
2a	68	90-92	light green	74.98 (74.96)	5.39 (5.22)	12.49 (12.49)	
2b	72	80-82	green	61.77 (61.48)	4.34 (4.04)	12.16 (12.40)	
2c	71	110-112	yellow	67.28 (67.27)	4.70 (4.76)	13.07 (13.10)	
2d	69	106-108	greenish white	69.31 (69.28)	4.92 (5.16)	18.64 (18.20)	
6a	73	260-262	orange	67.89 (67.93)	3.79 (4.12)	13.19 (13.19)	15.10 (14.83)
6b	70	242-244	brown	55.02 (54.60)	2.77 (2.76)	12.83 (12.83)	29.37 (28.86)
6c	71	226-228	dark brown	59.39 (59.10)	2.99 (3.23)	13.85 (13.85)	15.85 (16.05)
7[b]	71	82-84	yellow	55.97 (55.78)	4.02 (4.09)	18.65 (18.45)	21.34 (21.50)
8a	76	218-220	yellow	63.80 (63.74)	4.28 (4.33)	14.88 (14.93)	
8b	73	221-223	golden yellow	49.45 (49.50)	3.11 (3.10)	14.40 (14.30)	
8c	69	221-222	light brown	53.91 (53.71)	3.39 (3.38)	15.71 (15.60)	
11[c]	71	140-142	pale yellow	64.49 (64.84)	4.08 (4.08)	9.46 (9.45)	11.37 (10.81
13[d]	75	202-204	pale yellow	65.73 (65.43)	4.13 (4.32)	19.16 (19.12)	10.96 (10.81)

a) Lit[11]. m.p. 88-90°; b) MS (EI),m/z=150(M^+); c) MS (EI),m/z=296(M^+); d) MS (EI),m/z=292(M^+).

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TABLE 2. Spectral Data for Compounds **1a-d**, **2a-d**, **6a-c**, **7**, **8a-c**, **11** and **13** (IR, ^{1}H NMR and ^{13}C NMR)

Cmpd No	IR (cm^{-1})	^{1}H NMR (δ_H)	^{13}C NMR (δ_c)
1a[a]	1629 (CO)	2.99 (6H,s,$N(CH_3)_2$), 5.55 (1H, d, J = 12Hz, H-2) and 7.41-7.85 (6H, m, arom-H and H-3).	
1b[a]	1620 (CO)	2.98 (6H,s,$N(CH_3)_2$), 5.68 (1H, d, J = 12Hz, H-2) and 7.11-7.67 (4H,m,H-3and thienyl-H).	
1c[a]	1632 (CO)	3.00 (6H,s,$N(CH_3)_2$), 5.66 (1H, d, J = 12Hz, H-2), 6.43-6.49 (1H, m, furyl H-4), 7.02-7.07 (1H, m, furyl H-3), 7.46-7.49 (1H, m, furyl H-5) and 7.77 (1H, d, J = 12Hz, H-3).	
1d[a]	1630 (CO)	3.09 (6H,s,$N(CH_3)_2$), 6.47 (1H, d, J = 12Hz, H-2), and 7.20-8.80 (5H, m, H-3 and pyridyl-H).	
2a[a]	2215 (CN)	1.40 (3H, t, J = 8Hz, CH_3), 4.70 (2H,q, J = 8Hz, OCH_2) and 7.43-7.84 (7H, m, arom-H and pyridyl H-4 and H-5).	
2b[a]	2215 (CN)	1.30(3H, t, J = 8Hz, CH_3), 4.60 (2H,q, J = 8Hz, OCH_2) and 7.20-8.20 (5H, m, thienyl and pyridyl-H).	
2c[a]	2215 (CN)	1.50 (3H, t, J = 8Hz, CH_3), 4.50 (2H,q, J = 8Hz, OCH_2), 6.50 (1H, m, furyl H-4), 7.00-7.10 (1H, m, furyl H-3), 7.30 (1H, d, pyridyl H-4), 7.50 (1H, m, furyl H-5) and 7.90 (1H, d, pyrridyl H-5)	151.80 (C-2), 149.71 (C-6), 145.90; 144.47 (furyl C-2 and C-5), 144.00 (C-4), 115.37 (C-5), 112.73 (CN), 112.45 and 110.98 (furyl C-3 and C-4), 93.50 (C-3), 62.98 (OCH_2), and 14.18 (CH_3).
2d[a]	2215 (CN)	1.30 (3H, t, J = 8Hz, CH_3), 4.56(2H,q, J = 8Hz, OCH_2), and 7.25-8.73 (6H, m, pyridyl-H).	163.17 (C-6), 157.22 (C-2), 153.71 (C-2'), 150.01 (C-6'), 145.20 (C-4), 137.75 (C-4'), 125.68 (C-5'), 121.95 (C-3'), 115.8 (C-5), 113.55 (CN), 95.83 (C-3), 63.38 (OCH_2) and 14.60 (CH_3).

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TABLE 2. Continued

Cmpd No	IR (cm^{-1})	^1H NMR (δ_H)	^{13}C NMR (δ_c)
6a[b]	3440, 3150 (NH) and 2210 (CN)	7.75 (1H, d, *J* = 8Hz, H-5), 7.39-8.00 (5H, m, arom-H); 8.12 (1H, d, *J* = 8 Hz, H-4) and 14.15 (1H, br, NH).	179.16 (C-2), 154.00 (C-6), 145.17, 131.88, 129.18, 128.77 (aromatic carbons), 131.63 (C-4), 127.55 (C-5), 117.47 (CN) and 112.15 (C-3).
6b[b]	3420, 3145 (NH) and 2210 (CN)	7.05 (1H, d, *J* = 8 Hz, H-5), 7.22-7.33 (1H, m, thienyl H-4) and 7.93-8.20 (4H, m, H-4, NH and thienyl H-3 and H-5)	179.52 (C-2), 154.93 (C-6), 142.94, 142.64 , 132.53, 129.33, (thienylcarbons), 129.17 (C-4), 126.02 (C-5), 116.43 (CN) and 115.89 (C-3).
6c[b]	3440, 3155 (NH) and 2210 (CN)	6.76-6.83 (1H, m, furyl H-4), 7.08 (1H, d, *J* = 8 Hz, H-5), 7.87 (1H, d, *J* = 4 Hz, furyl H-3) and 8.01-8.11 (3H, m, H-4, NH and furyl H-5).	
7[a]	3445 (NH)	6.53 (1H, d, *J* = 5Hz, H-4), 7.00-7.61 (4H, m, H-5 and thienyl-H) and 11.20 (1H, br, NH)	144.44 (C-5), 136.64 (C-3), 131.66, 127.70, 124.60, 123.75, (thienylcarbons), 102.20 (C-4)
8a[b]	3445, 3115 (NH)	7.30-8.30 (7H, m, arom.-H and pyrimidyl-H), 13.60 (1H, br s, NH)	181.30 (C-2), 166.33 (C-4), 159.66 (C-6), 135.56, 132.66, 128-32, 127.40 (aromatic carbons) and 105.98 (C-5).
8b[b]	3455, 3113 (NH)	7.20-7.40 (2H, m, H-5 and thienyl H-4), 7.70-8.00 (3H, m, H-6 and thienyl H-3, and H-5) and 13.50 (1H, br, NH).	181.10 (C-2), 161.55 (C-4), 146.61 (C-6), 141.55, 134.89, 132.42, 129.39 (thienyl carbons) and 104.70 (C-5).
8c[b]	3470, 3105 (NH)	6.77-6.84 (2H, m, H-5 and furyl H-4), 7.12 (1H, d, *J* = 6Hz, H-6), 7.50-7.55 (1H, m, furyl H-3), 7.97-8.10 (1H, m, furyl H-5) and 13.40 (1H, br, NH).	
11[b]	1662 and 1615 (CO)	2.56 (3H, s, CH_3), 7.15-8.06 (8H, m, arom-H-and thienyl-H), 8.98 (1H, s, H-5)	
13[b]	1586 (C=N)	2.55 (3H, s, CH_3), 7.25-8.40 (8H, arom-H and thienyl-H), 9.74 (1H, s, H-3)	

a) In $CDCl_3$. b) In DMSO.

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1,2-Dihydro-4-substituted-pyrimidine-2-thiones (8a-c).- A mixture of each of **1a-c** (0.01 mol) and thiourea (0.02 mol, 0.76 g) in absolute ethanol (50 mL) was added to sodium ethoxide (0.6 g sodium metal in 60 mL of ethanol) and the mixture was refluxed for 8 hrs. Ethanol was distilled off and water was added to the residue. The aqueous solution was then neutralized with HCl. The solid product which formed, was collected by filtration and crystallized from ethanol.

3-Acetyl-1-phenyl-4-(2-thienoyl)-pyrazole (11).- A solution of **1b** (0.01 mol 1.89) in ethanol (30 mL) and **9** (1.96 g, 0.01 mol) was treated with 2 mL of triethylamine. The solution was left over night then refluxed for one hour. The solvent was then evaporated, and the remaining product was triturated with ethanol. The solid product which formed, was collected by filtration and crystallized from ethanol.

7-Methyl-2-phenyl-4-(2-thienyl)-(2H)-pyrazolo[3,4-d]pyridazine (13).- A mixture of **11** (0.01 mol 3.09) and hydrazine hydrate (0.01 mol, 0.5 mL) in ethanol (50mL) was refluxed for 4-5 hrs. The reaction mixture was concentrated under vacuum and left to cool. The solid product which formed, was filtered off and crystallized from ethanol.

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